Remarks

No new matter has been added by the amendment of the Specification.

I. Rejection Under 35 U.S.C. § 103

Claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-120 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Claeson, *Biochem J.* 290:309-312 (1993) (hereinafter "Claeson") in view of Skordalakes *J. Am. Chem. Soc.* 119: 9935-9936 (1997) (hereinafter "Skordalakes"), and further in view of Kettner, WO 94/21668 (hereinafter "Kettner"), Wienand, WO 97/05161 (hereinafter "Wienand") and /or Shoichet, WO 00/35904 (hereinafter "Shoichet").

Applicants respectfully traverse this rejection. A *prima facie* case of obviousness has not been established. First, even in combination, the cited art would not have suggested a parenteral formulation of a base addition salt of a boronic acid of formula (I) that binds to thrombin. Second, even assuming *arguendo* that the cited references were properly combinable, one of ordinary skill in the art would not have had reasonable expectation of success in arriving at the presently claimed invention, because he or she would have been led away from the claimed invention by the combined disclosures of the cited references.

Applicants reiterate their arguments already of record. Moreover, Applicants provide the following additional arguments, based on the evidence filed herewith in the form of the Kennedy Declaration.

The present invention provides parenteral pharmaceutical formulations comprising a pharmaceutically acceptable base addition salt of a peptidyl boronic acid as recited in the claims. The claimed parenteral pharmaceutical formulations are useful as thrombin inhibitors.

In order for a compound to be pharmaceutically useful as a thrombin inhibitor, it must have sufficient stability for an acceptable shelf life. Kennedy Declaration at ¶ 5. As Dr. Kennedy explains, the art, *i.e.*, Wu *et al.*, *J. Pharm. Sci. 89*: 758 (2000) (hereinafter "Wu"), which is of record in the present application, points away from converting a peptidyl boronic acid to its boronate salt, because Wu states *inter alia* alkaline conditions should not be favorable to stability. Kennedy Declaration at ¶ 21. However, salt manufacture involves exposing an acid to a base. Hence, as discussed in the remainder of the Kennedy Declaration, the cited art provides no reason for one of ordinary skill in the art to conclude that base addition salts of peptidyl boronic acids would be more stable than the corresponding free acid.

As Dr. Kennedy explains, the art teaches away from formulating peptidyl boronic acids as base addition salts and in favor of formulating them as esters in order to provide a stable formulation. Kennedy Declaration at ¶ 6. Moreover, although there are documented instances of peptidyl boronic acids and their esters being isolated as acid addition salts, they have not been isolated as base addition salts. *Id.*

Unlike ordinary peptides, peptidyl boronic acids are not carboxylic acids. Whereas an ordinary peptide contains a carboxyl group, a peptidyl boronic acid contains a boronyl group. Kennedy Declaration at ¶ 8. As Dr. Kennedy explains, peptidyl boronic acid chemistry presented him with unique difficulties, because boron does not

behave like carbon and presents some unusual challenges in pharmaceutical development. *Id.*

Compared to carboxylic acids, which are relatively stable, peptidyl boronic acids exhibit an inherent degradative instability of the boronyl group. Kennedy Declaration at ¶ 9. Owing to the $-B(OH)_2$ structure of peptidyl boronic acids, the peptidyl boronic acids can form diol stable esters, which carboxylic acids cannot form. *Id.* One example of such a boronic diol ester is the marketed formulation of peptidyl boronic acid N-(2-pyrazine) carbonyl-L-phenylalanine-L-leucine boronate, whose International Nonproprietary Name is bortezomib (previously known as MG-341). Kennedy Declaration at ¶ 24. Bortezomib as sold comprises the mannitol ester of the peptidyl boronic acid. *Id.* This peptidyl boronic acid is disclosed in Adams *et al.*, U.S. Patent No. 5,780,454 (hereinafter "Adams"), which is of record in the present application and is discussed below; in Wu; and in Gupta *et al.*, WO 02/059130 (hereinafter "Gupta"), which is also of record in the present application. Wu and Gupta disclose the instability of bortezomib, *id.* at ¶¶ 21-23, while Gupta points to esterification with a diol, in particular the lyophilized D-mannitol ester, as the route to stability. Kennedy Declaration at ¶ 23. Thus, remarkable changes in chemistry are afforded by replacing a carboxyl group (-COOH) with a boronyl group ($-B(OH)_2$). *Id.* at ¶ 9.

Given the physicochemical differences between carbon and boron, discussed by Dr. Kennedy in ¶¶ 8 and 9 of his declaration, one of ordinary skill in the art therefore would have been extremely cautious in extrapolating the physicochemical behavior of a carboxylic acid drug to draw any conclusions regarding the physicochemical behavior of a boronic acid drug. Kennedy Declaration at ¶ 10.

Within the class of compounds encompassed by the claimed invention is a base addition salt of a compound called TRI 50c, which is being developed as a candidate active pharmaceutical ingredient ("API") by the assignee of the present application, Trigen Limited. Kennedy Declaration at ¶ 11. TRI 50c is a second generation candidate API. *Id.* The first generation API was a pinacol ester of TRI 50c that was known as TRI 50b. *Id.* TRI 50c is the free acid of TRI 50b. Specification at page 9, line 35. TRI 50c has never been sold as a drug in any form. Kennedy Declaration at ¶ 12.

Turning to Claeson, Dr. Kennedy explains that Claeson mentions that although TRI 50 hydrolyzes spontaneously under physiological conditions, TRI 50c was, he believes, always isolated in the prior art as an ester, rather than as the free acid. Kennedy Declaration at ¶ 14. It is also helpful to examine Deadman *et al., J. Med. Chem 38*: 1511-1522 (1995) (hereinafter "Deadman"), which is of record in the present application. Dr. Kennedy explains that all of the compounds in Deadman are disclosed in the form of diol esters, specifically the pinanediol or pinacol ester. Kennedy Declaration at ¶ 14.

Dr. Kennedy agrees with the Examiner that it was previously known that esters of boronic acids can be de-esterified, and that ester forms of certain pharmaceutical compounds can hydrolyze under physiological conditions and thereby effectively act as prodrugs. Kennedy Declaration at ¶ 15. Dr. Kennedy also states that, while Wienand and Shoichet mention salts, the end products of their examples were free acids, and that the examples in Kettner describe acid addition salts. Kennedy Declaration at ¶ 16. As discussed by Dr. Kennedy, base addition salts were not made in any of these cited references. *Id.*

As Dr. Kennedy notes, peptidyl boronic acid salts are unstable and TRI 50c has significant stability problems, which make the molecule extremely difficult or impossible to put into a parenteral pharmaceutical formulation with adequate stability, *i.e.*, shelf-life, for practical use. Kennedy Declaration at ¶ 17. The claimed invention is thus directed to making parenteral pharmaceutical formulations. *Id.* The challenge for the inventors in the present application was to identify derivatives of peptidyl boronates which would be stable enough for pharmaceutical use. Kennedy Declaration at ¶ 18.

As Dr. Kennedy understands the Examiner's position, it would allegedly have been obvious to make base addition salts of any peptidyl boronic acids, for example, the peptidyl boronic acids of Adams, since it supposedly would have been obvious to try to make base addition salts. Kennedy Declaration at ¶ 19. One of the compounds discussed in Adams is N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid, which as discussed above is MG-341 (or bortezomib). *Id.* In Adams, pharmaceutical salts and esters are said to be "preferred." *Id.*

Dr. Kennedy reiterates, however, that the chemical behavior of boron is unique, and that at the time of filing of the present application, there was in his opinion no basis for supposing that base addition salts would be "preferred." Kennedy Declaration at ¶ 20. Indeed, later work on MG-341 related to a stable formulation of that compound as a mannitol ester, which points away from making a base addition salt. *Id.*

Wu also discusses MG-341 and teaches away from making a base addition salt of that compound. Citing Wu at page 758, Dr. Kennedy explains that Wu states:

> *The chemical stability of peptide boronic acid derivatives, from a formulation perspective, has not been extensively reported in the literature to our knowledge. During an effort to formulate 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ for*

> *parenteral administration, the compound showed erratic stability behaviour and was quite unstable in certain solvents.*

Kennedy Declaration at ¶ 21.

Citing Wu at page 763, Dr. Kennedy explains that Wu states:

> *Based on the known chemistry of boronic acids and the identity of the degradants, a degradation pathway of 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ was proposed and is illustrated in Scheme 1. The initial oxidation can be attributed to peroxides or molecular oxygen and its radicals.* ***Because light, metal ions and alkaline conditions normally facilitate oxidation these conditions should not be favorable to the stability of 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ or any other alkyl boronic acid derivative****. Consistent with this conclusion is the observation that light accelerated the degradation of 2-Pyz-(CO)-Phe-Leu B(OH)$_2$.* (Emphasis added).

Kennedy Declaration at ¶ 21.

Turning to Gupta, Dr. Kennedy explains that, while Gupta relates to a class of boronic acids, all the examples in Gupta describe 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$, *i.e.*, MG-341. Kennedy Declaration at ¶ 22. Gupta also acknowledges that boronic acids are unstable, as evidenced by their oxidization by air. *Id.* Gupta also discloses that, whereas the lyophilized D-mannitol ester of MG-341 was stable over a period of 18 months, the free acid was not stable for longer than 6 months. Kennedy Declaration at ¶ 23.

Dr. Kennedy further explains that MG-341, *i.e.*, bortezomib, is now sold under the trade name Velcade.® Kennedy Declaration at ¶ 24. A copy of the Velcade® package insert is attached to the Kennedy Declaration. As Dr. Kennedy explains, bortezomib is sold as a lyophilized powder of the mannitol ester of the free boronic acid. Kennedy Declaration at ¶ 24.

Elaborating on the chemistry of boronic acids, Dr. Kennedy explains that boric acid ($B(OH)_3$) is a weak acid. Kennedy Declaration at ¶ 25. The present application claims priority benefit of applications filed in Great Britain in September 2002. Therefore, in Dr. Kennedy's opinion, in September 2002, a chemist of ordinary skill in the art would have concluded that peptidyl boronic acids are weak acids, and that the salts of weak acids with strong bases form basic solutions. *Id.* Dr. Kennedy concludes that it would have been reasonable to predict that salts of peptidyl boronic acids with a strong base, such as sodium hydroxide, would form basic solutions. *Id.* As discussed above, however, according to Wu a basic solution would adversely affect stability. *Id.*

Dr. Kennedy also explains that in September 2002, one of ordinary skill in the art would have concluded that:

(1) peptidyl boronic acids are prone to oxidative degradation and, because light, metal ions and alkaline conditions normally facilitate oxidation (as disclosed in Wu), these conditions should not be favorable to stability;

(2) peptidyl boronic acids are weak acids and will form alkaline solutions with strong bases;

(3) base addition salts of peptidyl boronic acids had never been tested for their stability for formulating;

(4) but their esters had been tested (citing Gupta and the present assignee's work on TRI 50b);

(5) bortezomib was excessively unstable (citing Gupta and Wu); and

(6) bortezomib was stabilized by manufacture as an ester, namely its lyophilized D-mannitol ester, and not as a salt.

Kennedy Declaration at ¶ 26.

In Dr. Kennedy's view, at the time that the present application was filed, the facts relating to formulation of peptidyl boronic acids pointed firmly in the direction of making esters for stability, and base addition salts were unexplored. Kennedy Declaration at ¶ 27. One of ordinary skill reading about the destabilizing effect of alkaline conditions in Wu therefore would have been surprised to have learned that a peptidyl boronic acid could have been stabilized by combining the acid with alkali, to form a salt, and this view would have been further confirmed by the publication of the bortezomib package insert. *Id.* The prejudice against exposing a peptidyl boronic acid to alkaline conditions is specific to boronic acid chemistry, which is very different from the more mainstream carboxylic acid chemistry. Kennedy Declaration at ¶ 28.

In Dr. Kennedy's view, the ordinarily skilled worker would have had no reasonable expectation that base addition salts of the claimed peptidyl boronic acids would exhibit enhanced stability, because as discussed above Wu discloses that alkaline conditions favor oxidation, while formation of a salt from an acid requires addition of alkalai. Kennedy Declaration at ¶ 30. The cited art fails to recognize the challenges associated with shelf life and its associated requirement for adequate stability. *Id.* Moreover, the researchers who developed bortezomib decided to stabilize it by derivatization as a mannitol ester. *Id.* Finally, one of ordinary skill in the art would have been led by Wu away from the presently claimed base addition salts. *Id.*

Against Wu's teaching that peptidyl boronic acid salts would be unstable, the presently claimed invention counterintuitively achieves stability for the claimed class of peptidyl boronic acids by formulating them as boronate salts. Kennedy Declaration at ¶

31. To demonstrate this point, Dr. Kennedy discusses data attached to his declaration as Appendix A. The first part of Appendix A is a Summary Stability Report for the free acid TRI 50c, which shows in Table 1 that the free acid TRI 50c degraded dramatically over three months at 25°C, and shows in Table 2 that the purity of the free acid decreased from 97.18% to 58.83% over three months at 25°C. Kennedy Declaration at ¶ 31. The second part of Appendix A provides a Summary Stability Report for the TRI 50c sodium salt, which shows that after three months at 25°C, the purity of the TRI 50c sodium salt (*i.e.*, a base addition salt of the TRI 50c free acid) decreased only to 95.3%. Kennedy Declaration at ¶ 31.

The data in the stability report are consistent with the stability data obtained in Example 34 of the present application, in which sodium and lysine salts of peptidyl boronic acids were shown to be more stable than the free acid. Kennedy Declaration at ¶ 32. The data in the stability report are also consistent with the data reported in Example 28 of co-pending Application No. 10/659,178, which shows the encapsulated lysine salt to be more stable than the free acid, and with the data in Example 13 of U.S. Patent No. 7,112,572, which shows that the calcium salt of TRI 50c is more stable than the free acid. Kennedy Declaration at ¶ 32. Thus, Applicants have shown that several base addition salts of TRI 50c are more stable that the free acid.

As Dr. Kennedy explains, Wienand and Shoichet are not relevant to the presently claimed invention. Kennedy Declaration at ¶ 34. Dr. Kennedy concludes by stating again that Wu points away from combining boronic acid drugs with a base, because alkaline conditions are described as promoting instability, and Gupta points toward stabilizing boronic acid drugs as D-mannitol esters. Kennedy Declaration at ¶ 35. As a

result, one of ordinary skill in the art would have had no reason to expect that peptidyl boronic acid salts would provide enhanced stability of the parent acid. *Id.*

Applicants respectfully request that the obviousness rejection over Claeson, Skordalakes, Kettner, Wienand and Shoichet be reconsidered and withdrawn.

II. Additional Remarks

At page 44 of the Amendment and Reply filed in the present application on May 15, 2007, Applicants discussed Matteson *et al.*, U.S. Patent No. 5,681,978 (hereinafter "the Matteson '978 patent"), and pointed to column 4, lines 57-57, and stated that the Matteson '978 patent relates to oxidative resistance of a pinacol ester of a boronic acid. Upon subsequent review, Applicants now realize that this statement was made in error but inadvertently and without deceptive intent, since Applicants now understand that Matteson refers to oxidative resistance of a diol, not to an ester. Accordingly, Applicants respectfully wish to correct the record with respect to the disclosure of the Matteson '978 patent. Moreover, by the foregoing amendment, the incorrect description of the Matteson '978 patent has been deleted from the present Specification.

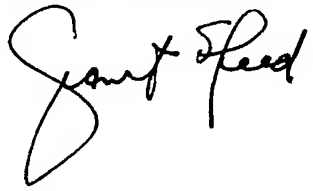
Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Date: September 28, 2007

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